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Attestation

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06.03.2001

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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.



Patentanmeldung Nr. Patent application No. Demande de brevet n°

99113502.1

PRIORITY DOCUMENT

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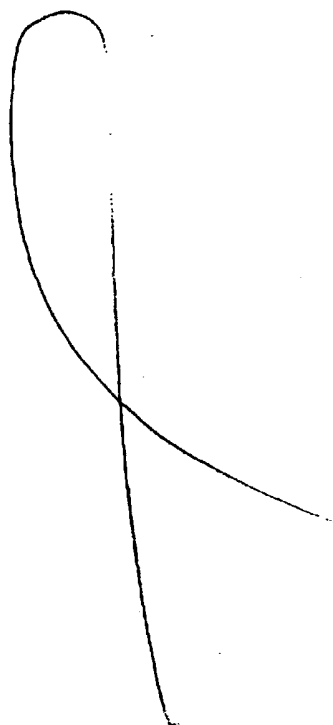
Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE, 29/05/00
LA HAYE, LE





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Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr
Application no
Demande n° 99113502.1

Anmeldetag
Date of filing
Date de dépôt 02/07/99

Anmelder
Applicant(s)
Demandeur(s)
Bayer Aktiengesellschaft
51368 Leverkusen
GERMANY

Bezeichnung der Erfindung
Title of the invention
Titre de l'invention
Angiotensin-7 and uses thereof

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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Internationale Patentklassifikation
International Patent classification:
Classification internationale des brevets

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Am Anmeldetag benannte Vertragsstaaten
Contracting states designated at date of filing AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LU/LU/MC/NL/PT/SE
Etats contractants désignés lors du dépôt

Bemerkungen
Remarks
Remarques

2

02 Juli 1999

Angiopoietin-7 and uses thereof

The present invention provides a nucleic acid molecule encoding human Angiopoietin-7 (Ang-7) protein. In addition the invention provides methods for producing recombinant human Ang-7 protein. The invention also provides an antibody which specifically binds human Ang-7 protein. The invention further provides for therapeutic compositions as well as a method for modulating angiogenesis.

Introduction

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The cellular behavior responsible for the development, maintenance, and repair of differentiated cells and tissues is regulated, in large part, by intercellular signals conveyed via growth factors and similar ligands and their receptors. The receptors are located on the cell surface of responding cells and they bind peptides of polypeptides known as growth factors as well as other hormone-like ligands.

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The phosphorylation of tyrosines on proteins by tyrosine kinases is one of the key modes by which signals are transduced across the plasma membrane. Several currently known protein tyrosine kinase genes encode transmembrane receptors for polypeptide growth factors and hormones.

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Growth factor receptors of endothelial cells are of particular interest due to the possible involvement of growth factors in several important physiological and pathological processes, such as vasculogenesis, angiogenesis, atherosclerosis, and inflammatory diseases. Also, the receptors of several hematopoietic growth factors are tyrosine kinases.

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Receptor tyrosine kinases differ in their specificity and affinity. In general, receptor tyrosine kinases are glycoproteins, which consist of (1) an extracellular domain capable of binding the specific growth factor(s); (2) a transmembrane domain which usually is an alpha-helical portion of the protein; (3) a juxtamembrane domain where

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- 2 -

the receptor may be regulated by, e.g., protein phosphorylation; (4) a tyrosine kinase domain which is the enzymatic component of the receptor; and (5) a carboxyterminal tail which in many receptors is involved in recognition and binding of the substrates for the tyrosine kinase.

5

A gene encoding an endothelial cell transmembrane tyrosine kinase, was described by Partanen, et al., Proc. Natl. Acad. Sci. USA, 87: 8913-8917 (1990). This gene and its encoded protein are called "Tie" which is an abbreviation for "tyrosine kinase with Ig and EGF homology domains." Partanen, et al. Mol. Cell. Biol. 12: 1698-1707 (1992).

10

Enhanced Tie expression was shown during neovascularization associated with developing ovarian follicles and granulation tissue in skin wounds. Korhonen, et al. Blood 80: 2548-2555 (1992). Thus, Tie has been suggested to play a role in angiogenesis, which is important for developing treatments for solid tumors and several other angiogenesis-dependent diseases such as diabetic retinopathy, psoriasis, atherosclerosis and arthritis.

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Two structurally related TIE receptor proteins have been reported to be encoded by distinct genes with related profiles of expression. Both genes were found to be widely expressed in endothelial cells of embryonic and postnatal tissues. Significant levels of Tie-2 transcripts were also present in other embryonic cell populations, including lens epithelium, heart epicardium and regions of mesenchyme. Maisonpierre, et al., Oncogene 8: 1631-1637 (1993).

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The predominant expression of the TIE receptor in vascular endothelia suggests that TIE plays a role in the development and maintenance of the vascular system.

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Two ligands, angiopoietin-1 (Ang-1) and-2 (Ang-2), have been identified for Tie-2. Angiopoietin-2 is antagonistic to angiopoietin-1, preventing binding of the activating ligand and blocking its ability to stimulate Tie-2 kinase activity and autophos-

- 3 -

phorylation. Angiopoietin-1 and -2 do not bind Tie-1. Angiopoietin-1 and -2 are about 60% identical. They share a similar domain structure with a N-terminal coiled-coil region and a C-terminal fibrinogen-like domain.

- 5 Northern analysis shows that angiopoietin-1 is quite widely expressed, but that the expression of angiopoietin-2 is very limited. It is present only in tissues such as ovary, uterus, and placenta, which undergo vascular remodeling.

- 10 Recently, two additional ligands for the Tie-2 receptor were identified (Valenzuela et al., Proc. Natl. Acad. Sci. 96: 1904-1909 (1999), Tie ligand-3 (angiopoietin-3 [Ang-3]) and Tie ligand-4 (angiopoietin-4[Ang-4]), but the precise physiological role of Ang 3 and 4 has not been reported yet. However, discovery of new members of the angiopoietin ligand family indicates that other members could exist.

- 15 Angiogenesis, concurrent with tissue development and regeneration, depends on the tightly controlled processes of endothelial cell proliferation, migration, differentiation and survival. Dysfunction of the endothelium is a key feature of many diseases including cancer, atherosclerosis, and diabetic angiopathies, to name but a few. Identification of novel Tie receptors and angiopoietins will shed light on the
.0 details of how blood vessels are generated, remodelled, and eliminated, thus, providing new tools to improve therapeutic standards to above mentioned indications.

- The invention is directed to the Ang-7 protein sequence, corresponding nucleic acid sequences, antibodies, pharmaceutical compositions, vectors and vector host
25 systems according to the claims.

Ang-7 protein as well as the Ang-7 antibodies can be used in the treatment of diseases as defined above.

Description of the figures.

Fig. 1: Nucleotide sequence encoding human Ang-7.

Fig. 2: Deduced amino-acid sequence of human Ang-7. The sequence is shown in the one letter code of amino-acids.

- 5 Fig. 3: Alignment of the amino acid sequences of Ang-1, Ang-2, Ang -3, Ang-4 and Ang-7. Identical amino acids are highlighted by boxes.

Fig. 4: Expression profile of Ang-7.

- Fig. 5: In vitro translation of Ang-7. Lane 1: Rainbow [¹⁴C]methylated protein molecular weight marker (Amersham, Little Chalfont Buckinghamshire, England) containing following proteins: ovalbumin (46 kDa), carbonic anhydrase (30 kDa),
10 trypsin inhibitor (21,5 kDa), lysozyme (14,3 kDa), aprotinin (6,5 kDa). Lane 2: In vitro translation of Ang-7 using the T7 promoter of the mammalian expression vector pcDNA3.1/Myc-His(-) (Invitrogen, Groningen, Netherlands). Lane 3: In vitro translation of Ang-7 using the SP6 promoter of the mammalian expression vector
15 pcDNA3.1/Myc-His(-) (negative control). Lane 4: Positive control from the in vitro translation system (Promega, Madison, USA).

Examples.**Example 1.**

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With the goal to identify new members of the angiopoietin ligand family a BLAST search (Altschul et al., 1997) of the Expressed Sequence Tag (EST) database from the National Center for Biotechnology Information (NCBI) has been performed. The amino acid sequence of Ang-1 was used as a probe. As a result, a human EST with the accession Number AA773234 was identified. The identified EST showed significant homology to Ang-1 in the reading frame +2. The P value (probability) was $4,4 \times 10^{-28}$ which strongly indicates that the identified EST encodes a fragment of a novel protein which could belong to the family of angiopoietins. Further proof that the newly identified EST encodes a fragment of a novel angiopoietin (lateron designated as Ang-7) was obtained when a BLAST search of a Swissprot database was performed using the identified EST as a probe. The P values obtained for Ang-1 and Ang-2 were $3,2 \times 10^{-32}$ and $2,6 \times 10^{-34}$, respectively.

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Because the commercial EST-clone providers were not able to deliver us the identified EST AA773234, we identified an other homologues EST which belongs to the same gene cluster. The corresponding EST-clone with the accession number AA255590 was purchased and analyzed. Sequencing analysis revealed that the clone AA255590 indeed encodes the fragment of the same gene and includes the sequence of EST AI773234.

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Example 2.

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For the purpose of full length cloning of the Ang-7 cDNA the HUCL primary membranes (Stratagene, La Jolla, USA) were hybridized with the antisense probe, prepared as described in the example 4. Hybridization revealed a signal at the position L04. The corresponding secondary array membrane was purchased and

hybridized under the same conditions. The signal was detected at the position G19. Thus, the individual clone L04G19 was purchased and analyzed. The clone contained an insert of 2,2 kb. Sequencing analysis confirmed, that this cDNA clone contains the full length coding sequence of Ang-7.

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Example 3.

Complete sequencing of the 2173 bp long L04G19 cDNA, which encodes Ang-7 (Seq ID 1, Fig. 1) revealed an open reading frame of 1432 bp which encodes a polypeptide of 493 amino acid residues (Seq. ID 2, Fig. 2). Alignment of the deduced amino acid sequence of Ang-7 with angiopoietins-1, -2, -3 and -4 is shown in Fig. 3. The N-terminal and C-terminal parts of the Ang-7 protein contain characteristic coiled-coil and fibrinogen - like domains, found also in other angiopoietins. The similarity index between the novel Ang-7 and Ang-1 and -2 is 23,9% and 23,5 %, respectively.

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Importantly, most of the amino acid residues which are conserved between known angiopoietins are also present in Ang-7 (Fig. 3). This indicates that the identified gene encodes a new member of the angiopoietin family.

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Example 4.

To study the expression profile of the identified novel Ang-7, the plasmid AA255590 was linearized with EcoRI and the antisense [³²P] radioactively labelled RNA probe was generated using Strip-EZ T3 kit (Ambion, Austin, USA) in accordance to the instructions of the manufacturer. An RNA master blot (Clontech Laboratories, Inc., Palo Alto, CA, USA) was hybridized with the generated probe. The hybridization and washing was performed as recommended in the manual of the Strip-EZ kit. After washing, the membrane was exposed to a phosphorimager screen, scanned on a Fuji Bas-1500 scanner, and the intensity of the radioactive signals was evaluated with the TINA 2.0 software (Raytest, Straubenhardt, Germany). The resulting histogram is

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presented on Fig. 4. The novel *ang-7* gene is strongly expressed in heart tissues (atrium left and right, ventricle left and right), uterus, mammary gland and corpus callusum.

- 5 Expression of Ang-7 in many tissues encompassing a high circulation of blood, indicates that Ang-7, as Ang-1 and -2, could play a role in angiogenesis.

Example 5.

- 10 To test whether the *ang-7* cDNA can be translated to Ang-7 protein and to determine the molecular weight of Ang-7, the complete cDNA was amplified by PCR and cloned upstream of the T7 promoter in the Eco RV and Kpn I restriction sites of the mammalian expression vector pcDNA3.1/Myc-His(-) (Invitrogen, Groningen, Netherlands). For PCR amplification, a 5' primer
- 15 (5' GCGAATTCACCATGAGGCCACTGTGCGT 3') homologous to the 5' end of the *ang-7* cDNA was used in combination with a 3' primer (5' GGAAGCTTATGGAAGGTGTTGGGGTTCGG 3') homologous to the 3' end of the Ang-7 cDNA. To increase translational efficiency a Kozak consensus sequence was integrated in the 5' primer. For cloning, recognition sequences for the restriction
- 20 enzymes Eco RV and Kpn I were introduced into the 5' and 3' primers, respectively. The in vitro translation was done essentially according to the instruction of the manufacturer (Promega, Madison, USA) using [³⁵S]methionine. The resulting reaction products were subjected to electrophoresis on a sodium dodecyl sulfate-12% polyacrylamide gel and visualized by autoradiography.
- 25 A major band of ~ 60 kDa was detected (Fig. 5). The observed molecular mass of the major band was slightly larger than the calculated molecular mass of recombinant Ang-7 (~57,1 kDa). However, since the amino acid sequence of Ang-7 contains several potential glycosylation sites the observed larger size of Ang-7 may be produced by incomplete glycosylation of the protein in the in vitro translation system.
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□

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110

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□

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□

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□

□

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□

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135

140

□

□

Val Glu Ala Gln Val Leu Asn Gln Thr Thr Arg Leu Glu Leu Gln Leu

□

145

150

155

160

□

□

Leu Glu His Ser Leu Ser Thr Asn Lys Leu Glu Lys Gln Ile Leu Asp

□

165

170

175

□

□

Gln Thr Ser Glu Ile Asn Lys Leu Gln Asp Lys Asn Ser Phe Leu Glu

□

180

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190

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□

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205

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- 18 -

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- 19 -

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- 22 -

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- 23 -

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☐ 50 55 60
☐
☐

-24-

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-25-

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- 26 -

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- 27 -

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☐

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☐☐

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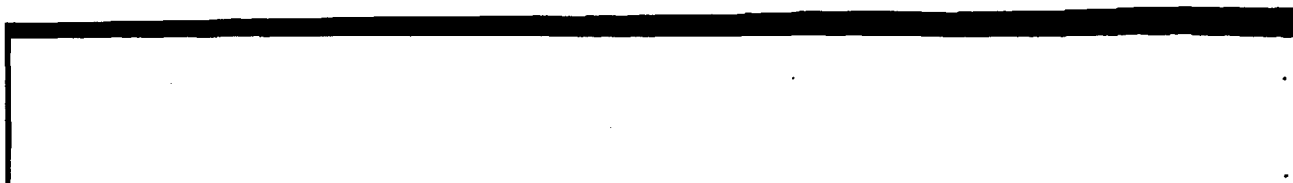
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☐

29

☐☐



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02. Juli 1999

Claims:

1. A polynucleotide comprising a member selected from the group consisting of:
 - 5 (a) a polynucleotide encoding the polypeptide as set forth in SEQ ID NO:2;
 - (b) a polynucleotide capable of hybridizing to and which is at least 70% identical to the polynucleotide of (a); and
 - (c) a polynucleotide fragment of the polynucleotide of (a) or (b).
- 10 2. The polynucleotide of claim 1 wherein the polynucleotide is DNA.
3. A vector containing one or more of the polynucleotides of claim 1 and 2.
- 15 4. A host cell containing the vector of claim 3.
5. A process for producing a polypeptide comprising: expressing from the host cell of claim 4 the polypeptide encoded by said DNA.
- 20 6. A polypeptide selected from the group consisting of
 - (a) a polypeptide having the deduced amino acid sequence of SEQ ID NO:2 and fragments, analogs and derivatives thereof, and
 - (b) a polypeptide comprising amino acid 1 to amino acid 493 of SEQ ID
- 25 NO:2.
7. A pharmaceutical composition comprising the polypeptide of claim 6.
8. An antibody capable to bind to the polypeptide of claim 6.
- 30 9. Use of the polypeptide of claim 6 for the preparation of medicaments.

- 29 -

10. A diagnostic kit for the detection of the polypeptide of claim 6.

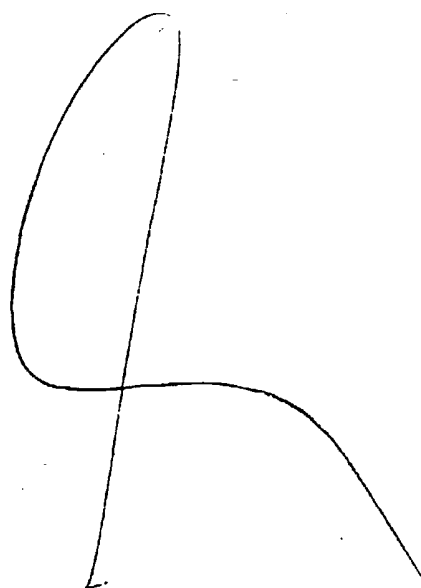
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EPO-Munich
53

02 Juli 1999

Angiopoietin-7 and uses thereof**Abstract**

The present invention provides an nucleic acid molecule encoding human Angiopoietin-7 (Ang-7) protein. In addition the invention provides methods for producing recombinant human Ang-7 protein. The invention also provides an antibody which specifically binds human Ang-7 protein. The invention further provides for therapeutic compositions as well as a method for modulating angiogenesis.



02 Juli 1999

Fig. 1: Sequence ID 1 (Ang-7)

GAAATGAGG CTGCTGCGGA CGCCTGAGG ATGACCCCA AGCCTGGAC CTGCCGAGCG TGGCACTGAG 70
GCAGCGGCTG ACGTACTGT GAGGGAAGA AGTTGTGAG CAGCCCCCA GGACCCCTGG CCAGCCCTGG 140
CCCCAGCTC TGCCGAGCC CTCTGTGGAG GCAGAGCCAG TGGAGCCAG TGAGGCAGGG CTGCTTGGCA 210
GCCACCGGCC TGCAACTCAG GAACCCCTCC AGAGGCCATG GACAGGCTGC CCGCTGACG GCCAGGGTGA 280
AGCATGTGAG GAGCCGCCCC GGAGCCAAGC AGGAGGGAAG AGGCTTTCAT AGATTCCTATT CACAAAGAAT 350
AACCACCATT TTGCAAAGAC CATGAGGCCA CTGTGCGTGA CATGCTGGTG GCTGGACTG CTGGCTGCCA 420
TGGGAGCTGT TGCAGGCCAG GAGGACGGT TTGAGGGCAC TGAGGAGGC TCGCCAAGAG AGTTCATTTA 490
CCTAAGCAGG TACAAGCGGG CGGGGAGTC CCAGGACAAG TGCACCTACA CCTTCATTGT GCCCCAGCAG 560
CGGCTACGG GTGCCATCTG CGTCAACTCC AAGGAGCCTG AGGTGCTTCT GGAGAACCGA GTGCATAAGC 630
AGGAGCTAGA GCTGCTCAAC AATGAGCTGC TCAAGCAGAA GCGGCAGATC GAGACGCTGC AGCAGCTGGT 700
AAGGTGGAC GCGGCATMG TGAGCGAGGT GAAGCTGCTG CCAAGGAGA GCGCAACAT GAAGTCGGG 770
GTCACGCAGC TCTACATGCA GCTCCTGCAC GAGATCATCC GCAAGCGGGA CAACGCGTTG GAGCTCTCCC 840
AGCTGGAGAA CAGGATCCTG AACCAGACAG CCGACATGCT GCAGCTGGCC AGCAAGTACA AGGACCTGGA 910
GCACAAGTAC CAGCACCTGG CCACACTGGC CCACAACCA TCAGAGATCA TCGGCGAGCT TGAGGAGCAC 980
TGCCAGAGGG TGCCCTCGGC CAGGCCGTC CCCCAGCCAC CCCCCTGTC CCGCCCCGG GTCTACCAAC 1050
CACCCACCTA CAACCGCATC ATCAACCAGA TCTTAACCA CGAGATCCAG AGTGACCAGA ACCTGAGGT 1120
GCTGCCACCC CCTCTGCCA CTATGCCAC TCTCAACAG CTCCATCTT CCACCGACAA GCGTCGGGC 1190
CCATGGAGAG ACTGCTGCA GGCCTGGAG GATGGCCAG ACACAGCTC CATCTACCTG GTGAAGCCGG 1260
AGAACACCA CGCCTCATG CAGGTGTGT GCGACCAGAG ACACGACCC GGGGGCTGGA CGTCTATCCA 1330
GAGACGCTG GATGGCTCTG TTAACCTCTT CAGGAACCTG GAGACGTACA AGCAAGGTT TGGGAACATT 1400
GACGGCGAAT ACTGGCTGG CCTGGAGAAC ATTTACTGGC TGAOGAACA AGGCAACTAC AACTCTCTGG 1470
TGACCATGGA GGACTGGTCC GCGCGCAAG TCTTGCAGA ATACGCCAGT TTCCGCTGG AACCTGAGAG 1540
CGAGTATTAT AAGCTGCGGC TGGGGCGCTA CCATGGCAAT GGGGTGACT CCTTTACATG GCACAACGGC 1610
AAGCAGTCA CCACCTGGA CAGAGATCAT GATGCTACA CAGGAACTG TGCCCACTAC CAGAAGGGAG 1680
GCTGGTGTA TAAGCCTGT GCCACTCCA ACCTCAACGG GTCTGGTAC CCGGGGGGCC ATTACCGGAG 1750
CGCTACCAG GACCGACTCT ACTGGGCTGA GTTCCGAGGA GGCTCTTACT CACTCAAGAA AGTGGTGATG 1820
ATGATCCGAC CGAACCCAA CACCTCCAC TAAGCCAGCT CCCCCTCTG ACCTCTCTG GCCATTGCCA 1890
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GGACCGGAT GCTGGATTCT GTTTCCGAA GTCAGTGCAG CGGATGATGG AACTGAATCG ATACGGTGT 2030
TTCTGTCCT CCTACTTCC TTCACACAG ACAGCCCTC ATGTCTCCAG GACAGGACAG GACTACAGAC 2100
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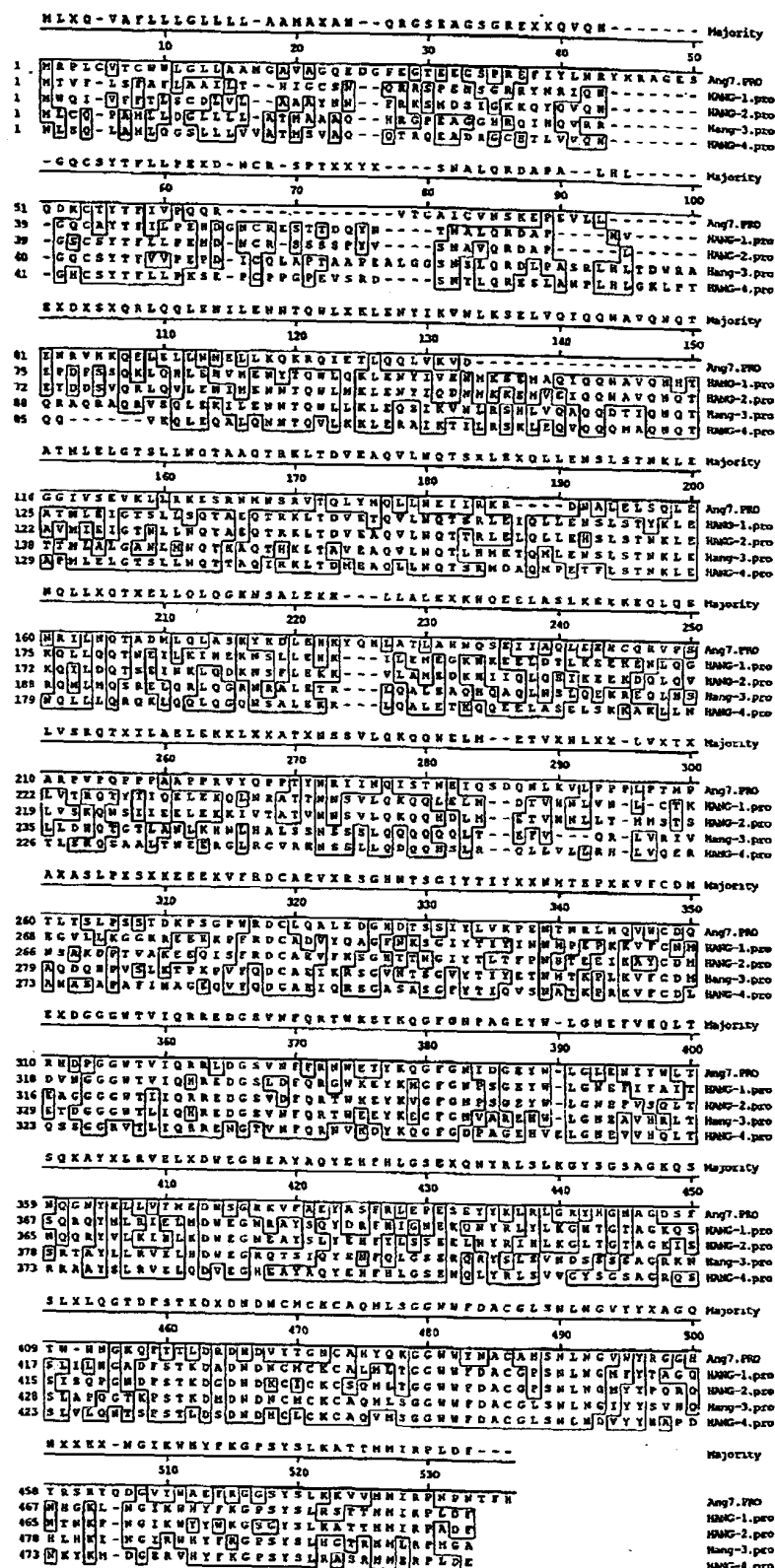
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Fig. 2: Sequence ID 2 (Ang-7)

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VNSKEPEVLL ENRVHKQELE LLNNELLKQK RQIETLQQLV KVDGGIVSEV KLLRKESRNM NSRVTQLYMQ 140
LLHEIIRKRD NALELSQLEN RILNOTADML QLASKYKDL EHYOHLATLA ENQSEIIAQL EEHCQVPSA 210
RPVQPQPPAA PPRVYQPPY NRIINQISTN EIQSDQNLKV LPPPLETMPT LTSLPSSTDK PSGFWRDCLQ 280
ALEDGHTSS IYLVKPENTN RLMQVWCDQR HDPGGATVIQ RRLDGSVNFT RNWETYKQGF GNIDGEYWLQ 350
LENIYWLTNQ GNYKLLVME DWSCRKVFAR YASFRLEPES EYKLRILGRY HGNAGDSEFW HNGKQFTILD 420
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TEH 493

9

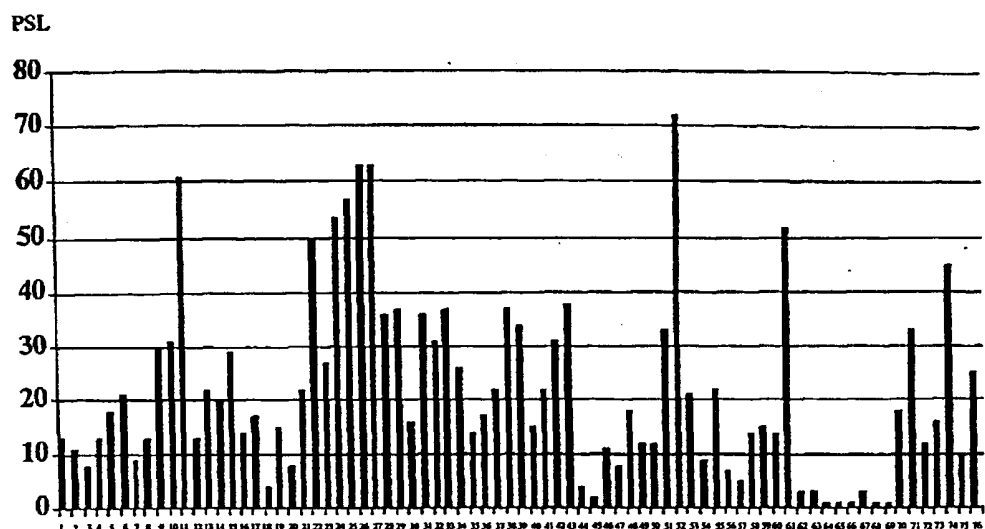
FIGURE 3



Decoration "Decoracion B1": Box residues that match the Consensus exactly.

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Expression profile of Angiopoietin 7



- 1- whole brain
- 2- cerebral cortex
- 3- frontal lobe
- 4- parietal lobe
- 5- occipital lobe
- 6- temporal lobe
- 7- paracentral gyrus of cerebral complex
- 8- pons
- 9- cerebellum left
- 10- cerebellum right
- 11- corpus callusum
- 12- amygdala
- 13- caudate nucleus
- 14- hippocalamus
- 15- medulla oblongata

- 35 -

16-putamen
17-substantia nigra
18-accumbens nucleus
19-thalamus
20-pituitary gland
21-spinal cord
22-heart
23-aorta
24-atrium left
25-atrium right
26-ventricle left
27-ventricle right
28-interventricular septum
29-apex of the heart
30-esophagus
31-stomach
32-duodenum
33-jejunum
34-ileum
35-ileocecum
36-appendix
37-colon ascending
38-colon transverse
39-rectum
40-kidney
41-skeletal muscle
42-spleen
43-thymus
44-peripheral blood
45-lymph node
46-bone marrow

- 36 -

47-trachea
48-lung
50-placenta
51-bladder
52-uterus
53-prostate
54-testis
55-ovary
56-liver
57-pancreas
58-adrenal gland
59-thyroid gland
60-salivary gland
61-mammary gland
62-Leukemia HL-60
63-HeLa S3
64-Leukemia K-562
65-Leukemia MOLT-4
66-Burkitt's lymphoma, Raji
67-Burkitt's lymphoma, Daudi
68-colorect. adenocarc. SW-480
69-Lung carcinoma A549
70-fetal brain
71-fetal heart
72-fetal kidney
73-fetal liver
74-fetal spleen
75-fetal thymus
76-fetal lung

Fig.4.

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Fig. 5

